HHS Public Access

Author manuscript

Am J Ophthalmol. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

Am J Ophthalmol. 2021 August ; 228: 212–219. doi:10.1016/j.ajo.2021.03.048.

Classification criteria for Sympathetic Ophthalmia

The Standardization of Uveitis Nomenclature (SUN) Working Group[*,1,2,3]

Abstract

Purpose: To determine classification criteria for sympathetic ophthalmia

Design: Machine learning of cases with sympathetic ophthalmia and 5 other panuveitides.

Methods: Cases of panuveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were split into a training set and a validation set.

[*]**Corresponding author:** Douglas A. Jabs, MD, MBA, Department of Epidemiology, the Johns Hopkins University Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205 Phone: 410-955-1254. djabs@jhmi.edu.

CRediT roles: Douglas A. Jabs, MD, MBA: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing--Review and editing, Visualization, Supervision, Project administration, Funding acquisition. **Andrew D. Dick, MBBS, MD, FRCP, FRCS, FRCOphth:** Investigation, Writing--Review and editing. **Michal Kramer, MD:** Investigation, Writing--Review and editing. **Cristina Muccioli, MD, PhD:** Investigation, Writing--Review and editing. **Neal Oden, PhD:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing--Review and editing. **Annabelle A. Okada, MD, DMSc:** Investigation, Writing--Review and editing. **Alan G. Palestine, MD:** Investigation, Writing--Original draft, Writing--Review and editing. **Narsing A. Rao, MD:** Investigation, Writing--Review and editing. **Russell W. Read, MD, PhD:** Investigation, Writing--Review and editing. **Jennifer E. Thorne, MD, PhD:** Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing--Review and editing. **Brett E. Trusko, PhD, MBA:** Methodology, Software, Resources, Data curation, Investigation, Writing--Review and editing.

[1]**Writing committee:** Douglas A. Jabs, MD, MBA[2,3]; Andrew Dick, MBBS, MD, FRCP, FRCS, FRCOphth[4–6]; Michal Kramer, MD[7]; Cristina Muccioli, MD, PhD[8]; Neal Oden, PhD[9]; Annabelle A. Okada, MD, DMSc[10]; Alan G. Palestine, MD[11]; Narsing A. Rao, MD[12]; Russell W, Read, MD, PhD[13]; Jennifer E. Thorne, MD, PhD[2,3],; Brett E. Trusko, PhD, MBA[14]

[2]**Affiliations:** [1]Members of the SUN Working Group are listed online at ajo.com. From [2]the Department of Epidemiology, the Johns Hopkins University Bloomberg School of Public Health, and [3]the Wilmer Eye Institute, the Department of Ophthalmology, the Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]the Academic Unit of Ophthalmology, Bristol Medical School, University of Bristol, Bristol, UK; [5]the National Institute for Health Research Biomedical research Centre at Moorfields Eye Hospital, London, UK; [6]University College London Institute of Ophthalmology, London UK; [7]the Department of Ophthalmology, Rabin Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [8]the Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil; [9]the Emmes Company, LLC, Rockville, MD, USA; [10]the Department of Ophthalmology, Kyorin University School of Medicine, Tokyo, Japan; [11]the Department of Ophthalmology, University of Colorado School of Medicine, Aurora, Co, USA; [12]the USC Roski Eye Institute, the Department of Ophthalmology, the University of Southern California School of Medicine, Los Angeles, CA, USA; [13]the Department of Ophthalmology, University of Alabama at Birmingham, Birmingham, AL, USA; [14]the Department of Medicine, Texas A&M University, College Station, TX, USA.

[3]**Conflict of Interest:** Douglas A. Jabs: none; Andrew Dick: consultant: AbbVie, Alimera, Apitope, Astellas, Gyroscope, Janssen, Roche; James P. Dunn: none; Michal Kramer: none; Cristina Muccioli: none; Neal Oden: none; Annabelle A. Okada: consultant: AbbVie Japan, Astellas Pharma Japan, Bayer AG, Daiichi Sankyo; lecture fees: Alcon Pharm Japan, Mitsubishi Tanabe Pharma, Novartis Pharma Japan, Santen Pharmaceutical Corporation, Senju Pharmaceutical Corporation; grant support from Alcon Pharma Japan, Bayer Yakuhin, Mitsubishi Tanabe Pharma; Alan G. Palestine: none; Narsing A. Rao: none; Jennifer E. Thorne: Dr. Thorne engaged in a part of this research as a consultant and was compensated for the consulting service; Brett E. Trusko: none.

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Machine learning using multinomial logistic regression was used on the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the panuveitides. The resulting criteria were evaluated on the validation set.

Results: One thousand twelve cases of panuveitides, including 110 cases of sympathetic ophthalmia, were evaluated by machine learning. The overall accuracy for panuveitides was 96.3% in the training set and 94.0% in the validation set (95% confidence interval 89.0, 96.8). Key criteria for sympathetic ophthalmia included bilateral uveitis with 1) a history of unilateral ocular trauma or surgery and 2) an anterior chamber and vitreous inflammation or a panuveitis with choroidal involvement. The misclassification rates for sympathetic ophthalmia were 4.2 % in the training set and 6.7% in the validation set, respectively.

Conclusions: The criteria for sympathetic ophthalmia had a low misclassification rate and appeared to perform sufficiently well for use in clinical and translational research.

PRECIS—Using a formalized approach to developing classification criteria, including informatics-based case collection, consensus-technique-based case selection, and machine learning, classification criteria for sympathetic ophthalmia were developed. Key criteria included bilateral uveitis with a history of unilateral ocular trauma or surgery and either anterior chamber and vitreous inflammation or panuveitis with choroidal involvement. The resulting criteria had a low misclassification rate.

Bilateral inflammation after unilateral eye trauma or surgery was first termed sympathetic ophthalmia by Mackenzie in 1840.[1] The ocular inflammation begins weeks to months or even years after an initiating traumatic ocular event, either physical trauma (most often a penetrating ocular injury) or intraocular surgery. The patient then develops bilateral inflammation in both the injured “exciting” eye and in the fellow “sympathizing” eye. Classically, sympathetic ophthalmia was described as a “granulomatous” (i.e. with mutton fat keratic precipitates) panuveitis, but with the advent of modern therapy, full-blown disease may not always be seen. Hence some patients may not have “granulomatous” features and may have minimal anterior chamber inflammation.[2–7]

Sympathetic ophthalmia is a rare disease, which has been declining in incidence. It is estimated to occur in 0.02% to 0.05% of cases of ocular trauma and 0.01% of cases of ocular surgery, typically multiple ocular surgeries, particularly vitreoretinal surgery.[2,4] A prospective surveillance study in the United Kingdom estimated the incidence as 0.03/100,000/year.[5] In this series, ocular surgery was a more frequent cause than traumatic ocular injury.[5] Although nearly all cases occur after penetrating ocular injury or intraocular surgery, sympathetic ophthalmia after trans-scleral laser to the ciliary body, pan-retinal photocoagulation, and radiation therapy for choroidal melanoma has been described, albeit rarely. [2–7]

Sympathetic ophthalmia is by definition a bilateral uveitis, but observation of inflammation in the exciting eye may be prevented by prior enucleation, phthisis, or corneal opacity. In the era before modern microsurgery and corticosteroid therapy, enucleation of the injured eye typically was performed to prevent sympathetic ophthalmia, and sometimes of the “exciting” eye to improve outcomes in the “sympathizing” eye (a controversial practice), but the low incidence of sympathetic ophthalmia, improvements in globe-preserving surgery,

and improvements in therapy largely have led to discontinuation of these practices.[5] Clinical features on ocular examination include anterior chamber inflammation, keratic precipitates, vitreous inflammation, multifocal choroidal infiltrates, and uncommonly serous retinal detachment.[2–7] The choroidal lesions present as multifocal, small, subretinal yellow-white spots, and are known histologically as Dalen-Fuchs nodules. In later stages of the disease the multifocal choroidal lesions become areas of chorioretinal atrophy with loss of retinal pigment epithelium. These lesions are hyperfluorescent on fluorescein angiography and hypofluorescent on indocyanine green angiography.[8] Similar choroidal lesions can be seen in late-stage Vogt-Koyanagi-Harada disease, sometimes termed Dalen-Fuchs-like nodules, and sarcoidosis. Optic disc edema is a recognized complication, and optical coherence tomographic imaging or ultrasound may demonstrate choroidal thickening.[8]

The histopathology of sympathetic ophthalmia demonstrates an inflammatory infiltrate with mononuclear inflammatory cells (lymphocytes and macrophages) and classically multinucleated giant cells with granuloma formation. Not all cases have granuloma formation, and some cases have only an inflammatory infiltrate of lymphocytes, both T and B cells. Dalen-Fuchs nodules, not found in all cases, are composed of lymphocytes, histiocytes, and de-pigmented retinal epithelial cells.[9,10] HLA-DR expression can be detected on retinal pigment epithelial cells,[11] leading to speculation about their role in the inflammatory process and as possible antigen presenting cells. However, the pathologic features are similar to other granulomatous eye diseases, such as sarcoidosis.[10]

The Standardization of Uveitis Nomenclature (SUN) Working Group has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification. Among the diseases studied was sympathetic ophthalmia.[12–18]

Methods

The SUN Developing Classification Criteria for the Uveitides project proceeded in four phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning[14–16,18]

Informatics.

As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and the development of a standardized, menu-driven hierarchical case collection instrument.[14]

Case collection and case selection.

De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease as previously described.[16,18] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database using formal consensus techniques described in the accompanying article.[16,18] Because the goal was to develop classification criteria,[17] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (i.e. were “selected”).[16,18]

Machine learning.

The final database then was randomly separated into a training set (~85% of cases) and a validation set (~15% of cases) for each disease as described in the accompanying article.[18] Machine learning was used on the training set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the training set and the validation set, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm when compared to the consensus diagnosis.[18] For sympathetic ophthalmia, the diseases against which it was evaluated were: Vogt-Koyanagi-Harada (VKH) disease (both early-stage and late-stage), Behçet disease uveitis, sarcoidosis-associated panuveitis, syphilitic panuveitis, and tubercular panuveitis.

Comparisons of subsets of cases with sympathetic ophthalmia.

Cases with and without choroidal nodules (“Dalen-Fuchs nodules”) and cases with penetrating ocular trauma vs ocular surgery were compared with the chi-square test or the Fisher’s exact test if a cell was <5 for categorical variables and the Wilcoxon rank sum test for continuous variables. P-values were nominal and two-sided.

The study adhered to the principles of the Declaration of Helsinki. Institutional Review Boards (IRBs) at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual IRBs.

Results

One hundred forty-nine cases of sympathetic ophthalmia were collected and 110 (71%) achieved supermajority agreement on the diagnosis during the “selection” phase and were used in the machine learning phase. These cases of sympathetic ophthalmia were compared to 806 cases of other uveitides, including 194 cases of Behçet disease, 156 cases of early-stage VKH, 103 cases of late-stage VKH, 102 cases of sarcoidosis-associated panuveitis, 70 cases of syphilitic panuveitis, and 277 cases of tubercular panuveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[18] The characteristics at presentation to a SUN Working Group Investigator of cases with sympathetic ophthalmia are listed in Table 1. A comparison of cases due to multiple ocular surgeries only vs those due to penetrating ocular injury is presented as Table 2. Traumatic cases were younger and more often male. There was an apparent shift in the distribution of vitreous cells to higher grades among those with multiple ocular surgeries, but no difference in vitreous haze. Cases of sympathetic ophthalmia due to multiple ocular surgeries also were more likely to have exudative detachments and sunset glow fundus, although these features occurred in a minority of cases in both subsets. The comparison of cases with and without choroidal lesions is presented as Table 3. Cases with choroidal lesions were more likely to be chronic and have either no or mutton fat keratic precipitates. The criteria developed after machine learning for sympathetic ophthalmia are listed in Table 4. The overall accuracy for panuveitides was 96.3% in the training set and 94.0% in the validation set (95% confidence interval 89.0, 96.8).[18] The misclassification rates for sympathetic ophthalmia were 4.2% in

the training set and 6.7% in the validation set. The disease with which SO most often was confused was tubercular panuveitis.

Discussion

The classification criteria developed by the SUN Working Group for sympathetic ophthalmia have a low misclassification rate, indicating good discriminatory performance against other panuveitides.

Sympathetic ophthalmia is considered the prototypical ocular autoimmune disease. Trauma or surgery allows either exposure of an ocular antigen in a privileged site or abrogation of tolerance resulting in autoimmune inflammation in both eyes.[3,8] Injury to the eye, either penetrating trauma or surgery (typically multiple surgeries), is the *sine qua non* for diagnosis. Classically described as a bilateral “granulomatous” panuveitis, it has become evident that in the modern treatment era the spectrum of disease is broader. Bilateral uveitis is necessary for diagnosis but may not always be observable; nevertheless when both eyes can be examined, bilateral disease is necessary for diagnosis. However, mutton fat keratic precipitates, which are the hallmark of what clinicians call “granulomatous uveitis”, were present in a minority of patients (10%), and choroidal lesions in 63%. As such, some cases with an anterior and intermediate uveitis were considered by a supermajority of the selection committee to have sympathetic ophthalmia. Consistent with other reports,[2–7] patients with sympathetic ophthalmia after ocular trauma were younger and more likely to be male. There was a suggestion that cases of sympathetic ophthalmia after multiple ocular surgeries without penetrating injury might have a more severe vitritis, as evidence by the distribution of vitreous cells, but there was no difference between the two subsets in the distribution of vitreous haze. Cases with choroidal lesions were more likely to be chronic, suggesting that the more “severe” disease may be related to chronicity. However, no cases of an isolated anterior uveitis were diagnosed as sympathetic ophthalmia. Whether sympathetic ophthalmia can present as an isolated anterior uveitis cannot be addressed from these data, and the criteria exclude isolated anterior uveitis as sympathetic ophthalmia at this time.

An overlap in clinical features between sympathetic ophthalmia and Vogt-Koyanagi-Harada disease has previously been described, including exudative retinal detachments and sunset glow fundus in a minority of patients with sympathetic ophthalmia,[2–8] leading to speculation about shared pathogenetic pathways. Indeed exudative retinal detachments (the classic ocular feature of early-stage Vogt-Koyanagi-Harada disease) were present in 18% of cases, and sunset glow fundus (the classic ocular feature of late-stage Vogt-Koyanagi-Harada disease) in 10% of cases of sympathetic ophthalmia. In these cases, it is the history of ocular trauma that distinguishes between the two diseases.

The presence of any of the exclusions in Table 4 suggests an alternate diagnosis, and the diagnosis of sympathetic ophthalmia should not be made in their presence. In prospective studies many of these tests will be performed routinely, and the alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of these tests may have been performed. Hence the presence of an exclusionary criterion excludes sympathetic

ophthalmia, but the absence of such testing does not always exclude the diagnosis of sympathetic ophthalmia if the criteria for the diagnosis are met.

Classification criteria are employed to diagnose individual diseases for research purposes.[17] Classification criteria differ from clinical diagnostic criteria, in that although both seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[17] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients without the disease in question that might confound the data. The machine learning process employed did not explicitly use sensitivity and specificity; instead it minimized the misclassification rate. Because we were developing classification criteria and because the typical agreement between two uveitis experts on diagnosis is moderate at best,[16] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement on the diagnosis. As such, some cases which clinicians would diagnose with sympathetic ophthalmia will not be so classified by classification criteria, such as the issue of isolated anterior uveitis discussed above.

In conclusion, the criteria for sympathetic ophthalmia outlined in Table 4 appear to perform sufficiently well for use as classification criteria in clinical research.[17,18]

Acknowledgments

Grant support: Supported by grant R01 EY026593 from the National Eye Institute, the National Institutes of Health, Bethesda, MD, USA; the David Brown Fund, New York, NY, USA; the Jillian M. And Lawrence A. Neubauer Foundation, New York, NY, USA; and the New York Eye and Ear Foundation, New York, NY, USA.

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Table 1.

Characteristics of Cases with Sympathetic Ophthalmia

Characteristic	Result
Number cases	110
Demographics	
Age, median, years (25^{th} 75^{th} percentile)	43 (25, 59)
Gender (%)	
Men	67
Women	33
Race/ethnicity (%)	
White, non-Hispanic	61
Black, non-Hispanic	4
Hispanic	2
Asian, Pacific Islander	15
Other	9
Missing	9
Uveitis History	
Uveitis course (%)	
Acute, monophasic	18
Acute, recurrent	1
Chronic	72
Indeterminate	9
Ophthalmic examination	
Keratic precipitates (%)	
None	59
Fine	23
Round	8
Stellate	0
Mutton Fat	10
Other	0
Anterior chamber cells (%)	
Grade 0	16
½+	19
1+	25
2+	25
3+	12
4+	3
Hypopyon (%)	2
Anterior chamber flare (%)	
Grade 0	33

Characteristic	Result
1+	35
2+	21
3+	9
4+	2
Iris in the sympathizing eye (%)	
Normal	83
Posterior synechiae	17
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
Intraocular pressure (IOP), involved eyes	
Median, mm Hg (25^{th}, 75^{th} percentile)	14 (10, 16)
Proportion patients with IOP>24 mm Hg either eye (%)	4
Vitreous cells (%)	
Grade 0	18
½+	25
1+	29
2+	20
3+	7
4+	1
Vitreous haze (%)	
Grade 0	48
½+	19
1+	15
2+	10
3+	5
4+	2
Exudative retinal detachment (%)	18
Sunset glow fundus (%)	10
Dalen Fuchs nodules (multifocal choroiditis) (%)	63
Ocular Trauma (%)	
Multiple ocular surgeries	45
Penetrating ocular injury	39
Penetrating ocular injury followed by multiple ocular surgeries	16

Table 2.

Comparison of Cases with Multiple Ocular Surgeries only vs Cases with Penetrating Ocular Injury

Characteristic	Multiple Ocular Surgeries	Penetrating Ocular Injury*	P-value
Number cases	50	60	
Demographics			
Age, median, years (25th 75th percentile)	58 (40, 71)	35 (18, 44)	<0.0001
Gender (%)			0.012
Men	54	77	
Women	46	23	
Race/ethnicity (%)			0.15
White, non-Hispanic	61	61	
Black, non-Hispanic	2	5	
Hispanic	0	3	
Asian, Pacific Islander	20	10	
Other	3	16	
Missing	14	5	
Uveitis History			
Uveitis course (%)			0.59
Acute, monophasic	20	18	
Acute, recurrent	1	0	
Chronic	74	70	
Indeterminate	6	12	
Ophthalmic examination			
Keratic precipitates (%)			0.07
None	50	66	
Fine	25	22	
Round	8	8	
Mutton Fat	18	3	
Anterior chamber cells (%)			0.41
Grade 0	10	22	
½+	16	22	
1+	30	19	
2+	28	24	
3+	14	10	
4+	2	3	
Hypopyon (%)	2	2	1.00
Anterior chamber flare (%)			0.51
Grade 0	26	39	
1+	34	36	

Characteristic	Multiple Ocular Surgeries	Penetrating Ocular Injury*	P-value
2+	26	17	
3+	12	7	
4+	2	2	
Iris in the sympathizing eye (%)			0.60
Normal	86	80	
Posterior synechiae	14	20	
Intraocular pressure (IOP), involved eyes			
Median, mm Hg (25^{th}, 75^{th} percentile)	14 (9, 16)	14 (10, 16)	0.92
Percent patients with IOP>24 mm Hg either eye	4	4	1.00
Vitreous cells (%)			0.01
Grade 0	12	22	
½+	12	36	
1+	46	19	
2+	24	17	
3+	6	5	
4+	0	2	
Vitreous haze (%)			0.37
Grade 0	40	54	
½+	20	19	
1+	18	14	
2+	16	5	
3+	4	7	
4+	2	2	
Exudative retinal detachment (%)	36	17	0.02
Sunset glow fundus (%)	18	2	0.01
Dalen Fuchs nodules (multifocal choroiditis) (%)	62	63	0.94

*Includes eyes with penetrating ocular injury followed by multiple ocular surgeries

Table 3.

Comparison of Cases with Choroidal Lesions versus Cases without Choroidal Lesions

Characteristic	Choroidal Nodules	No Choroidal Nodules	P-value
Number cases	69	41	
Demographics			
Age, median, years (25^{th} 75^{th} percentile)	44 (23, 59)	43 (28, 60)	0.88
Gender (%)			0.39
Men	69	61	
Women	31	39	
Race/ethnicity (%)			0.24
White, non-Hispanic	70	49	
Black, non-Hispanic	5	2	
Hispanic	0	5	
Asian, Pacific Islander	9	22	
Other	10	7	
Missing	6	15	
Uveitis History			
Uveitis course (%)			0.01
Acute, monophasic	9	32	
Acute, recurrent	0	2	
Chronic	83	54	
Indeterminate	8	12	
Ophthalmic examination			
Keratic precipitates (%)			0.001
None	70	41	
Fine	13	39	
Round	4	15	
Mutton Fat	13	5	
Anterior chamber cells (%)			0.14
Grade 0	22	7	
½+	20	17	
1+	26	22	
2+	23	29	
3+	7	20	
4+	1	5	
Hypopyon (%)	3	0	0.39
Anterior chamber flare (%)			0.20
Grade 0	36	27	
1+	36	34	
2+	22	20	

Characteristic	Choroidal Nodules	No Choroidal Nodules	P-value
3+	6	15	
4+	0	5	
Iris in the sympathizing eye (%)			0.89
Normal	84	80	
Posterior synechiae	16	20	
Intraocular pressure (IOP), involved eyes			
Median, mm Hg (25th, 75th percentile)	14 (10, 18)	14 (11, 16)	0.87
Proportion patients with IOP>24 mm Hg either eye	6	3	0.67
Vitreous cells (%)			0.07
Grade 0	26	5	
½+	22	29	
1+	26	34	
2+	17	24	
3+	7	7	
4+	1	0	
Vitreous haze (%)			0.58
Grade 0	49	46	
½+	16	24	
1+	13	20	
2+	12	7	
3+	7	2	
4+	3	0	
Exudative retinal detachment (%)	19	36	0.04
Sunset glow fundus (%)	10	10	1.00
Ocular Trauma (%)			
Multiple ocular surgeries only	46	46	1.00
Penetrating ocular injury *	54	54	1.00

* Includes cases with penetrating ocular injury followed by multiple ocular surgeries.

Table 4.

Classification Criteria for Sympathetic Ophthalmia

Criteria
1. History of unilateral ocular trauma or surgery
AND
2. Ocular inflammation, either
a. Bilateral OR
b. If there is no view in the inciting eye (e.g. enucleated, phthisis, opaque cornea), then detectable inflammation in the sympathizing eye
AND
3. Evidence of more than isolated anterior uveitis, either
a. Anterior chamber and vitreous inflammation OR
b. Panuveitis with choroidal involvement
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Evidence for sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata)